

- 60 -

Claims:

1. An isolated, synthetic or recombinant χ -conotoxin peptide having the ability to inhibit neuronal amine transporter comprising the following sequence of amino acids:

5

Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys .

SEQ ID NO. 3

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;

10 or a sequence in which Gly, Tyr, Lys or Leu are subject to conservative amino acid substitution or side chain modification;

with the proviso that the peptide is not χ -MrIA, χ -MrIB, Mar2, CMrVIA, Bn1.5, Mr1.3 or Au1.4;

or a salt, ester, amide, prodrug or cyclised derivative thereof.

15

2. An isolated, synthetic or recombinant χ -conotoxin peptide having the ability to inhibit neuronal amine transporter comprising the following sequence of amino acids:

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

20

SEQ ID NO. 4

where

Xaa1 is selected from Trp, DTrp, Tyr, Phe, hPhe, Ala, MeY, Arg, Ben, Nap, Orn, pGlu, DpGlu and a deletion;

25 Xaa2 is selected from Arg, Ala, Asn, Lys, Phe, BHK, Orn, Lys, DArg, Nle, DLys, DMK, DAsn, Thr, ABZ, Nap, Cit, Val, Tyr, Trp, pGlu, DpGlu or a deletion;

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle, Ser or Phe;

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala, Asn, Trp, Phe and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;

30

- 61 -

or a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino acid substitution or side chain modification;
with the proviso that the peptide is not χ -MrIA, χ -MrIB, Mar2, Mr1.3 or Au1.4;
and or a salt, ester, amide, prodrug or cyclised derivative thereof.

5

3. An isolated, synthetic or recombinant χ -conotoxin peptide having the ability to inhibit neuronal amine transporter comprising the following sequence of amino acids:

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

10

SEQ ID NO. 4

where Xaa1 is selected from Trp, Tyr, Phe, hPhe, Ala, MeY, Arg, Ben and Nap,

Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK, DAsn, Thr, ABZ, Nap, Cit and Val,

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

15

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;

or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino acid substitution or side chain modification,

20

or a salt, ester, amide, prodrug or cyclised derivative thereof.

4. An isolated, synthetic or recombinant χ -conotoxin peptide having the ability to inhibit neuronal amine transporter consisting of the following sequence of amino acids:

25

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQ ID NO. 4

where Xaa1 is selected from Trp, Tyr, Phe, hPhe, Ala, MeY, Arg, Ben and Nap,

Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK, DAsn, Thr, ABZ, Nap, Cit and Val,

30

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

- 62 -

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys,
or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino acid substitution or side chain modification or a salt, ester,
5 amide or prodrug thereof.

5. An isolated, synthetic or recombinant χ -conotoxin peptide comprising the following sequence of amino acids:

10 Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 5
where Xaa1 is an N-terminal residue and is selected from pGlu, DpGlu, Pro, Hyp or an N-acetylated amino acid residue;
Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK, DAsn, Thr, ABZ, Nap, Cit, Val and a deletion,
15 Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,
Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and
Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;
or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are
20 subject to conservative amino substitution or sidechain modification, or a salt, ester, amide or prodrug thereof.

6. An isolated, synthetic or recombinant χ -conotoxin peptide consisting of the following sequence of amino acids:

25 Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 5
where Xaa1 is an N-terminal residue and is selected from pGlu, Pro, Hyp or an N-acetylated amino acid residue;
30 Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK, DAsn, Thr, ABZ, Nap, Cit, pGlu, Val and a deletion,

- 63 -

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;

5 or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino and substitution or said chain modification, or a salt or prodrug thereof.

7. An isolated, synthetic or recombinant χ -conotoxin peptide having the ability to
10 inhibit neuronal amine transporter comprising the following sequence of amino acids:

Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 6

where Xaa2 is BHK, Orn, Arg, DArg or DMK;

15 Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;

or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are
20 subject to conservative amino acid or side chain modification, or a salt, ester, amide, prodrug or cyclised derivative thereof.

8, An isolated, synthetic or recombinant χ -conotoxin peptide having the ability to
inhibit neuronal amine transporter consisting of the following sequence of amino acids:

25

Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 6

where Xaa2 is BHK, Orn, Arg, DArg or DMK;

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser;

30 Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu; and

- 64 -

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;

or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino acid or side chain modification, or a salt, ester, amide, 5 prodrug or cyclised derivative thereof.

9. The peptide of any one of claims 2 to 4 wherein Xaa1 is Trp, Tyr or hPhe.
10. The peptide of claim 9 wherein Xaa1 is Trp.
- 10 11. The peptide of any one of claims 2 to 4, 9 or 10 wherein Xaa2 is Arg, Lys or Asn.
12. The peptide of claim 5 or 6 wherein Xaa1 is pGlu or DpGlu.
- 15 13. The peptide of any one of claims 5, 6 or 12 wherein Xaa2 is a deletion.
14. The peptide of claim 5 or 6 wherein Xaa2 is BHK or Orn.
15. The peptide of any one of claims 2 to 14 wherein Xaa3 is Gly or Asp.
- 20 16. The peptide of claim 15 wherein Xaa3 is Gly.
17. The peptide of any one of claims 2 to 16 wherein Xaa4 is Leu, Nle or Val.
- 25 18. The peptide of any one of claims 2 to 17 wherein Xaa5 is selected from His, Arg, Trp, Nal, Glu and a deletion.
19. The peptide of claim 18 wherein Xaa5 is Arg or His.
- 30 20. The peptide of any one of claims 2 to 19 wherein Xaa6 is selected from Hyp, Pro, Ala, Tic, Pip, MeY, DMD, Phe, THZ, Glu, Nle, Tyr and a deletion.

- 65 -

21. The peptide of claim 20 wherein Xaa6 is Hyp or Pro.
22. The peptide of any one of claims 1 to 21 wherein the Tyr of loop 1 has been
5 replaced with MeY.
23. The peptide of any one of claims 1 to 22 wherein the Leu of loop 1 is replaced
with Hle or Nle.
- 10 24. The peptide of any one of claims 1 to 23 having from 11 to 20 amino acids.
25. An isolated, synthetic or recombinant χ -conotoxin peptide as set forth in Table 2.
26. An isolated, synthetic or recombinant peptide as set forth in Table 3, excluding
15 SEQ ID NO. 1 and 7.
27. The peptide of any one of claims 1 to 26 with the ability to selectively inhibit
neuronal noradrenaline transporter, and has negligible or no substantial
anticholinergic effect.
- 20 28. A composition comprising an isolated, synthetic or recombinant χ -conotoxin
peptide having the ability to inhibit neuronal noradrenaline transporter, wherein
said χ -conotoxin peptide comprises the following sequence of amino acids:
- 25 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 3

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except
Cys, or such a sequence in which loop1 residues Gly, Tyr, Lys or Leu are subject to
conservative amino acid substitution or side chain modification, with the proviso that the
30 peptide is not χ -MrIA or χ -MrIB; or a salt, ester, amide, prodrug or cyclised derivative
thereof,

- 66 -

and a pharmaceutically acceptable carrier or diluent.

29. The composition of claim 28 wherein the peptide is as defined in any one of
5 claims 2 to 27.

30. The composition of claim 28 or 29 having one or more active agents in addition to
the peptide.

10 31. Use of an isolated, synthetic or recombinant χ -conotoxin peptide having the ability
to inhibit neuronal noradrenaline transporter, wherein said χ -conotoxin peptide comprises
the following sequence of amino acids:

Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQ ID NO. 3

15

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except
Cys, or such a sequence in which loop 1 residues Gly, Tyr, Lys or Leu are subject to
conservative amino acid substitution or side chain modification, with the proviso that the
peptide is not χ -MrIA or χ -MrIB; or a salt, ester, amide, prodrug or cyclised derivative
20 thereof,

20

in the manufacture of a medicament for the treatment or prophylaxis of urinary or
cardiovascular conditions or diseases, or mood disorders, or for the treatment or control of
pain or inflammation.

25

32. The use of claim 31 wherein the peptide is as defined in any one of claims 2 to 27.

33. Use of the peptides of any one of claims 1 to 27 or compositions of any one of
claims 28 to 30 as inhibitors of neuronal noradrenaline transporter, or in the treatment or
30 prophylaxis of diseases or conditions in relation to which the inhibition of neuronal
noradrenaline transporter is associated with effective treatment.

- 67 -

34. The use as defined in claim 33 in the treatment or prophylaxis of urinary or cardiovascular conditions or diseases or mood disorders or for the treatment or control of pain or inflammation.

5 35. A method for the treatment or prophylaxis of urinary or cardiovascular conditions or diseases or mood disorders or for the treatment or control of pain or inflammation including the step of administering to a mammal an effective amount of an isolated, synthetic or recombinant χ -conotoxin peptide having the ability to inhibit neuronal noradrenaline transporter, wherein said χ -conotoxin peptide comprises the following
10 sequence of amino acids:

Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQ ID NO. 3

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except
15 Cys, or such a sequence in which Gly, Tyr, Lys or Leu are subject to conservative amino acid substitution or side chain modification, with the proviso that the peptide is not χ -MrIA or χ -MrIB; or a salt, ester, amide, prodrug or cyclised derivative thereof.

36. The method of claim 35 wherein the peptide is as defined in any one of claims 2 to
20 27.

37. The method of claim 35 or 36 wherein the peptide is administered substantially simultaneously or sequentially with other active agents useful in the treatment of the conditions, diseases or disorders.
25